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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,183	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *112-120,123-130,133-140 and 143-150* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *112-120,123-130,133-140 and 143-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 9/30/2009.

2. Currently Claims 112-120, 123-130, 133-140, 143-150 are pending. Claims 1-111, 121-122, 131-132, and 141-142 are cancelled.

3. The following rejections for Claims 112-120, 123-130, 133-140, 143-150 are newly applied as necessitated by amendment or reiterated. Specifically the rejections presented below have been amended to discuss the amendments to the claims and the newly presented claims.

4. This action is final

Terminal Disclaimer

5. The terminal disclaimer filed on 1/21/2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 10/718391 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Withdrawn Rejections

6. The objection to the claims 141-142 made in section 5 is moot based upon the cancellation of the claims.

7. The rejection of the claims under 35 USC 112/2nd paragraph made in section 7 of the previous office action is moot based upon amendments to the claims.

8. The rejection of the claims under 35 USC 112/New Matter made in section 8 is withdrawn based upon in view of applicant's remarks on page 13-14 with regard to RNase H activity of reverse transcriptase.

Information Disclosure Statement

9. The information disclosure statement (IDS) submitted on 9/30/09 has been considered by the examiner. The reference of "Definition for transcription, prokaryotic transcription, eukaryotic transcription from wikipedia" was cross through as the cited reference fails to meet all the requirements set forth in MPEP 609 as the office action does not have an actual publication date. However, the reference has nevertheless been considered by the examiner. A copy of the IDS with the examiners initials and date has been provided along with this office action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 112-120, 123-130, 143-145, 149-150 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheele (US Patent 5162209 November 10, 1992).

With regard to Claim 112, step a, Scheele teaches providing a first DNA strand (e.g. a DNA molecule of interest) (column 3 lines 25).

With regard to step b, Scheele teaches contacting the DNA with dNTPs (e.g. nucleic acid precursors) (Column 4 lines 20-22). Scheele teaches a primer comprising an RNA segment (Column 3 lines 33-40). Scheele teaches a method of adding E. coli DNA polymerase I (e.g. effective amount of nucleic acid producing catalyst) (column 4 lines 14-15). Scheele teaches a method of adding RNase H (Column 4 lines 25).

With regard to step c, Scheele teaches a method of carrying out synthesis in the presence of the RNA primer to generate a polynucleotide comprising an RNA/DNA hybrid (Column 3 lines 30-40 and Figure 5).

With regard to step d, Scheele teaches a method of digesting the substrate with RNase H to remove the ribonucleic acid segment of the extended primer (Column 3 lines 30-40, column 4 lines 25-28, and Figure 5). Scheele teaches that the method can by adapted to permit amplification of the sample of dsDNA by PCR methodology (column 8 lines 58-60). Scheele teaches that the reagents of the RNA primer, DNA target, dNTPs and Taq are placed into a PCR machine with the appropriate number of PCR temperature cycles (column 8 lines 65-69). Therefore in a PCR cycle the resultant dsDNA of step c would be denatured such that the strands of DNA produced which are identical to the DNA of interest can be used in the PCR cycle to produce more copies of the DNA of interest.

With regard to Claim 113, Scheele teaches that the primers comprise unmodified nucleotides because Scheele teaches the primers comprise nucleotides (Figure 5 step 3).

With regard to Claim 114, Scheele teaches that the primer includes a portion with that is complementary to an oligonucleotide tail added to the 3' end of the target DNA template (column 3 lines 25-35). Therefore the primers include a sequence which is complementary to the tail and therefore not complementary to the sequence of the DNA molecule of interest (e.g. the tail is added to the DNA target of interest but the tail is not considered the DNA which is of interest to be amplified) (Figure 5 and column 3 lines 25-40).

With regard to Claim 115, Scheele teaches that the primers comprise at least 5 nucleotides (column 3 lines 56-57).

With regard to Claim 116, Scheele teaches that the primer can include DNA and RNA because Scheele teaches that only some of the nucleotides of the primer are RNA (Column 3 lines 40-45).

With regard to Claim 117, Scheele teaches that the nucleic acid producing catalyst is a DNA polymerase (column 4 lines 14-15).

With regard to Claim 118, Scheele teaches that the DNA polymerase is E. coli DNA polymerase I (Column 4 lines 14-15).

With regard to Claim 119, Scheele teaches that the polymerase can also include Taq polymerase (Column 8 lines 66).

With regard to Claim 120, Scheele teaches that the nucleic acid precursors can be labeled (column 8 lines 37-38).

With regard to Claim 123, step a, Scheele teaches providing a first DNA strand (e.g. a DNA molecule of interest) (column 3 lines 25).

With regard to step b, Scheele teaches contacting the DNA with dNTPs (e.g. nucleic acid precursors) (Column 4 lines 20-22). Scheele teaches a primer comprising an RNA segment and a DNA segment by teaching that some of the nucleotide sequence of the primer is an RNA sequence and therefore the rest of the nucleotides would be DNA (e.g. a copolymer primer) (Column 3 lines 33-40). Scheele teaches a method of adding E. coli DNA polymerase I (e.g. effective amount of nucleic acid producing catalyst) (column 4 lines 14-15). Scheele teaches a method of adding RNase H (Column 4 lines 25).

With regard to step c, Scheele teaches a method of carrying out synthesis in the presence of the RNA primer to generate a polynucleotide comprising an RNA/DNA hybrid (Column 3 lines 30-40 and Figure 5).

With regard to step d, Scheele teaches a method of digesting the substrate with RNase H to remove the ribonucleic acid segment of the extended primer (Column 3 lines 30-40, column 4 lines 25-28, and Figure 5). Scheele teaches that the method can by adapted to permit amplification of the sample of dsDNA by PCR methodology (column 8 lines 58-60). Scheele teaches that the reagents of the RNA primer, DNA target, dNTPs and Taq are placed into a PCR machine with the appropriate number of PCR temperature cycles (column 8 lines 65-69). Therefore in a PCR cycle the resultant

dsDNA of step c would be denatured such that the strands of DNA produced which are identical to the DNA of interest can be used in the PCR cycle to produce more copies of the DNA of interest.

Scheele teaches a method of adding excess primer (e.g. multiple copies of the copolymer primer) (Column 8 lines 58-60). Scheele et al. teaches that once the dsDNA is generated RNase H is used to remove the RNA primer (column 9 lines 1-5). Therefore once the RNA segment from the primer is removed the template is used to amplify another target strand by using another copolymer primer.

With regard to Claim 124, Scheele teaches that the primers comprise unmodified nucleotides because Scheele teaches the primers comprise nucleotides (Figure 5 step 3).

With regard to Claim 125, Scheele teaches that the primer includes a portion that is complementary to an oligonucleotide tail added to the 3' end of the target DNA template (column 3 lines 25-35). Therefore the primers include a sequence which is complementary to the tail and therefore not complementary to the sequence of the DNA molecule of interest (Figure 5 and column 3 lines 25-40).

With regard to Claim 126, Scheele teaches that the primers comprise at least 5 nucleotides (column 3 lines 56-57).

With regard to Claim 127, Scheele teaches that the nucleic acid producing catalyst is a DNA polymerase (column 4 lines 14-15).

With regard to Claim 128, Scheele teaches that the DNA polymerase is E. coli DNA polymerase I (Column 4 lines 14-15).

With regard to Claim 129, Scheele teaches that the polymerase can also include Taq polymerase (Column 8 lines 66).

With regard to Claim 130, Scheele teaches that the nucleic acid precursors can be labeled (column 8 lines 37-38).

With regard to Claim 143, step a, Scheele teaches providing a first DNA strand (e.g. a DNA molecule of interest) (column 3 lines 25).

With regard to step b, Scheele teaches contacting the DNA with dNTPs (e.g. nucleic acid precursors) (Column 4 lines 20-22). Scheele. teaches a primer comprising an RNA segment and a DNA segment by teaching that some of the nucleotide sequence of the primer is an RNA sequence therefore the primer sequence would include DNA (e.g. a copolymer primer) (Column 3 lines 33-40). Scheele teaches a method of adding E. coli DNA polymerase I (e.g. effective amount of nucleic acid producing catalyst) (column 4 lines 14-15). Scheele teaches a method of adding RNase H (Column 4 lines 25).

With regard to step c, Scheele teaches a method of carrying out synthesis in the presence of the RNA primer to generate a polynucleotide comprising an RNA/DNA hybrid (Column 3 lines 30-40 and Figure 5). The instant specification does not define isostatic conditions of temperature, buffer and ionic strength. Scheele teaches combining the primer and the DNA molecule in a reagent solution at a particular heat with buffers that have a particular ionic strength to produce at least one copy of the DNA molecule by extension of the primer (Column 8 lines 1-15). Therefore Scheele teaches

a method of allowing the mixture to react under isostatic condition of temperature, buffer, and ionic strength.

With regard to step d, Scheele teaches a method of digesting the substrate with RNase H to remove the ribonucleic acid segment of the extended primer (Column 3 lines 30-40, column 4 lines 25-28, and Figure 5). Scheele teaches that the method can by adapted to permit amplification of the sample of dsDNA by PCR methodology (column 8 lines 58-60). Scheele teaches that the reagents of the RNA primer, DNA target, dNTPs and Taq are placed into a PCR machine with the appropriate number of PCR temperature cycles (column 8 lines 65-69). Therefore in a PCR cycle the resultant dsDNA of step c would be denatured such that multiple copies of the DNA could be copied from the DNA of interest.

With regard to Claim 144, Scheele teaches that the primer can include DNA and RNA (Column 3 lines 40-45).

With regard to Claim 145, Scheele teaches that the primer includes a portion with is complementary to an oligonucleotide tail added to the 3' end of the target DNA template (column 3 lines 25-35). Therefore the primers include a sequence which is complementary to the tail and therefore not complementary to the sequence of the DNA molecule of interest (e.g. the tail is added to the DNA target of interest) (Figure 5 and column 3 lines 25-40).

With regard to Claim 149, Scheele et al. teaches that a label can be added to the dinucleotides mixture (e.g. the nucleic acid precursors) (column 7 lines 50-51).

With regard to Claims 150, Scheele et al. teaches that the primer includes a portion with that is complementary to an oligonucleotide tail added to the 3' end of the target DNA template (column 3 lines 25-35). Therefore the primers include a sequence which is complementary to the tail and therefore not complementary to the sequence of the DNA molecule of interest (e.g. the tail is added to the DNA target of interest but the tail is not considered the DNA which is of interest to be amplified) (Figure 5 and column 3 lines 25-40). Therefore Scheele et al. teaches a polynucleotide primer that comprises at least 1 noncomplementary nucleotide.

Response to arguments

The reply traverses the rejection. A summary of the arguments made in the reply are summarized below with response to arguments following.

(a) The reply asserts that the method described by Scheele intrinsically requires an additional step where a primer is bound artificially to a DNA molecule by a ligation step or terminal transferase extension, whereas the reply asserts that such a step is missing in the applicant's invention and claim 112 (p. 21 1st full paragraph of arguments).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that the claimed steps are of the comprising language which indicates that additional methods steps could be included. Herein in the instant case, this addition step would be encompassed by the claimed method. As stated above the

method of Scheele et al. produces more than one copy of the DNA molecule of interest and teach all the recited steps.

(B) The reply asserts that there is an important distinction between the instant invention and the method of Scheele which can be seen in Scheele's figure 5 (p. 21 1st full paragraph of arguments). The reply asserts that in Figure 5, RNase H digestion is used to remove an RNA primer, but the newly exposed single stranded region is not used for binding of another RNA primer, but rather it is digested with a single strand specific exonuclease thereby preventing any subsequent primer binding events (p. 21 1st full paragraph of arguments).

The reply assert that there is therefore no description in Scheele for preserving the single stranded segment that is generated by the treatment of an RNA primer with RNAse H so that more binding and extension events can take place to generate more copies of the nucleic acid (p. 22 1st paragraph). The reply asserts that teachings of Scheele would not allow such an event to take place because the exonuclease is present at the same time as the RNase H, eliminating the primer biding site that would be needed for binding of a second RNA primer (p. 22 1st paragraph). The reply asserts that the step before the RNase H step entails the inactivation of Pol I which would render the polymerase incapable of using the RNA primer to make a second copy (p. 22 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be asserting that claim 112 requires the same primer binding even to occur, however, the claim has not been limited to such a step. Specifically step d requires digestion with RNase H wherein the removal allows for another DNA molecule to be produced. Herein in the instant case, Scheele et al. teaches the amplification via PCR. Scheele et al teaches a sample of ds cDNA is prepared and added to its RNA primer with its DNA tail extension intact and excess RNA primers and excess oligo(dT). Taq and dNTPs are further added. The mixture is then subjected to PCR and then RNAse is added. As such Scheele et al. teach that multiple copies of the DNA molecule of interest are produced. The applicant seems to be asserting that the main difference between Scheele et al. and the claimed method is that the claim method requires the addition of RNase H before multiple copies are produced. However, the claim has a larger breadth than this limitation. Step d only requires the digestion of the substrate with RNase H so that the substrate is capable of another primer binding event to occur. The wherein clause does not limit the last step to a positive recitation of removing the RNA segment with RNase H and then producing another DNA molecule by performing steps a-d.

(C) The reply points to column 2 (19) of the '926 application which states "the regeneration of a primer binding site thereby allows a new priming event to occur and the production of more than one copy of said specific nucleic acid (p. 22 2nd paragraph). The reply asserts that a priming event would be considered to be both the binding of a primer to its complementary site as well as extension and consequently a second

priming event results in synthesis of a second copy (p. 22 2nd paragraph). The reply asserts that although Scheele describes the use of an RNA primer, he teaches away for this priming event because he carries out a step that prevents second binding events after RNase H digestion (p. 22 3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

As stated above, the claims are not limited to production of the second copy of the nucleic acid by the steps of a-d. Rather the claims are limited to production of multiple copies of the nucleic acid and the digestion with RNase H. Herein it is the position of the examiner that the claims are not limited to such a recitation of positive active steps. Further it is not clear where the applicant is pointing to with the recitation of the '926 application as this application does not appear to be either the application number of the instant application or the application number of Scheele et al. However it is noted that the claims are not limited to particular priming events, but rather the wherein clause merely requires that the removal step will have the property or the ability of another primer binding event to occur.

(D) The reply asserts that step d has been amended to specifically claim other binding events by claiming “digesting said substrate with RNase H to remove said ribonucleic acid segment of said extended primer, wherein said removal allows another priming event to occur with said nucleic acid of interest" (p. 22 last paragraph –p. 23 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

As stated above, the claims are not limited to production of the second copy of the nucleic acid by the steps of a-d. Rather the claims are limited to production of multiple copies of the nucleic acid and the digestion with RNase H. Herein it is the position of the examiner that the claims are not limited to such a recitation of positive active steps. Further it is not clear where the applicant is pointing to with the recitation of the '926 application as this application does not appear to be either the application number of the instant application or the application number of Scheele et al. However it is noted that the claims are not limited to particular priming events, but rather this wherein statement does not require any active process to occur, it merely requires that the removal step will have the property or the ability of another primer binding event to occur.

(E) The reply asserts that therefore there is no description of a denaturation step after step c in the steps recited for claim 112 and therefore the steps cited by the office action are completely different than the claimed step d (p. 23 2nd full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The claims are drawn to a process comprising the steps of a-d. Therefore the steps could have additional steps not cited. Herein in the instant case, Scheele et al. has a step of denaturation, but Scheele et al. still digests with RNase H and produces multiple copies of said nucleic acid. As such the method of Scheele et al. teaches all the required positive active steps of the claim.

(F) With regard to Claim 114, the reply asserts that the claim has an additional limitation wherein the primer is now required to have two segments, a first segment that is complementary to a sequence in the DNA of interest (similar to the conditions of claim 112) and a second segment that are not complementary (p. 23 last paragraph). The reply asserts that the homopolymeric primers of Scheele cannot be used to encompass both types of sequences (p. 23 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be asserting that the primers of Scheele et al have been characterized by the examiner as both homopolymeric and comprising noncomplementary sequences. However, this is not the case for Scheele et al. Rather Scheele et al teaches a primer that comprises a RNA segment (Column 3 lines 33-40) and it includes a portion that is complementary to an oligonucleotide tail added to the 3' end of the target DNA template (column 3 lines 25-35). Therefore the primer would comprise a sequence complementary to a distinct sequence of the DNA molecule of interest. Herein in Scheele it would be the RNA segment which is complementary. Further it would comprise a portion which is noncomplementary to the DNA of interest. The 3' end is not complementary to the DNA molecule of interest but rather complementary to the tail portion which is added to the DNA. Therefore the primers of Scheele are taught to be partially complementary to a distinct sequence of the DNA molecule and partially noncomplementary.

(G) The reply asserts that with reference to page 7 and comments on claim 123, the same remarks which have been stated with regard to claim 112 are maintained (p. 24 1st full paragraph). The reply asserts that on p. 8 of the office action there is a more complete description of the adapted PCR method of Scheele, but that is an alternative methodology wherein the use of RNase H has been eliminated and the primer removal is carried out by the PCR (p. 24 3rd paragraph). The reply asserts that the RNase H step is only added by Scheele after amplification in conjunction with exonuclease and it is not responsible itself for any amplification but only trimming the PCR product (p. 24 3rd full paragraph). The reply asserts that therefore Scheele actually teaches that once a target strand has been amplified by another polymer, the RNA segment from the primer is removed and that there is no description in the Scheele reference of any amplification taking place after the RNase H step (p. 25 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Again these arguments are drawn to the interpretation of step d. It is noted that the wherein clause does not require any active process to occur, it merely requires that the removal step will have the property or the ability of another primer binding event to occur. Step d does not specifically require amplification after digesting, but rather requires digestion and multiple copies to be produced. Therefore the teachings of Scheele et al. provide all the limitations of the positive active steps of the claims.

(H) The reply asserts that the term isostatic is used herein to be akin to isothermal conditions, but the exact parameters need not be described (p. 25 2nd paragraph-p. 27 1st paragraph).

These arguments have been fully reviewed

The examiner agrees that the exact parameters need not be described and the examiner was addressing the breadth of the term in the office action, but the term has not been rejected under 112/2nd with regard to indefiniteness.

(I) The reply assets that with regard to p. 13 of the previous office action and step d of claim 146, as previously discussed the claim has been amended to disclose that the RNase H is used to produce more than one copy which is not taught by Scheele et al. (p. 27 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that this claim is actually rejected under 35 USC 103(a), presented below. However, since the arguments are cited in the arguments towards the 35 USC 102 they are addressed here.

With regard to claim 146, step c of the claim includes producing at least one copy of the DNA molecule by extension of the primer under isostatic conditions and then step d is removing the ribonucleotides from the RNA segment by reverse transcriptase to regenerate the primer binding site on said DNA molecule and thereby produce more than one copy of the DNA molecule. The applicant seems to be asserting that the production of the multiple DNA copies is preformed in step d after the addition of the

reverse transcriptase, however, based on the teaches of step c it appears that the DNA copies are produced in step c. The way the claim is written encompasses a interpretation that the DNA copies are made in step c (e.g. the PCR step of Scheele et al) and then the RNA is removed to regenerate the primer binding site (e.g. the step of RNase H of Scheele et al). Therefore although the primer binding site is available to another binding event, the multiple copies are actually produced in step c. Step d does not require that another copy of the DNA molecule be produced after the addition of the reverse transcriptase.

(J) The reply asserts with regard to p. 13 and the comments concerning claim 146 the Scheele primer is considered to be complementary to the DNA of interest because the DNA of interest includes the added tail and for purposes of being described by claim 148, the Scheele primer is not considered in the office action to be complementary to the DNA of interest since it is now defined as not including the added tail, as such the reply asserts that there is inconsistent definition provided by the office action (p. 27 3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be asserting that the primers of Scheele et al have been characterized by the examiner as both homopolymeric and comprising noncomplementary sequences. However, this is not the case for Scheele et al. Rather Scheele et al teaches a primer that comprises a RNA segment (Column 3 lines 33-40) and it includes a portion that is complementary to an oligonucleotide tail added to the 3'

end of the target DNA template (column 3 lines 25-35). Therefore the primer would comprise a sequence complementary to a distinct sequence of the DNA molecule of interest. Herein in Scheele it would be the RNA segment which is complementary. Further it would comprise a portion which is noncomplementary to the DNA of interest. The 3' end is not complementary to the DNA molecule of interest but rather complementary to the tail portion which is added to the DNA. Therefore the primers of Scheele are taught to be partially complementary to a distinct sequence of the DNA molecule and partially noncomplementary.

Claim 146 is drawn to primers which are "substantially complementary" but this term is not defined in the specification. As such the primer of Scheele et al. would encompass such a structure because the only part that is not complementary is the region that hybridizes to the 3' tail.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 146-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheele (US Patent 5162209 November 10, 1992) in view of Schuster et al. (US Patent 5169766 December 8, 1992).

With regard to Claim 146, step a, Scheele teaches providing a first DNA strand (e.g. a DNA molecule of interest) (column 3 lines 25).

With regard to step b, Scheele teaches contacting the DNA with dNTPs (e.g. nucleic acid precursors) (Column 4 lines 20-22). Scheele. teaches a primer comprising an RNA segment and a DNA segment by teaching that some of the nucleotide sequence of the primer is an RNA sequence such that the rest of the sequence would be DNA (e.g. a copolymer primer) (Column 3 lines 33-40). Scheele teaches a method of adding E. coli DNA polymerase I (e.g. effective amount of nucleic acid producing catalyst) (column 4 lines 14-15). Scheele teaches a method of adding RNase H (Column 4 lines 25). Therefore Scheele teaches a method of adding a polymerase and RNase H to the sample and does not teach adding a reverse transcriptase having RNase H activity.

With regard to step c, Scheele teaches a method of carrying out synthesis in the presence of the RNA primer to generate a polynucleotide comprising an RNA/DNA hybrid (Column 3 lines 30-40 and Figure 5). The instant specification does not define isostatic conditions of temperature, buffer and ionic strength. Scheele teaches combining the primer and the DNA molecule in a reagent solution at a particular heat with buffers which would have particular ionic strength to produce at least one copy of the DNA molecule by extension of the primer (Column 8 lines 1-15).

With regard to step d, Scheele teaches a method of digesting the substrate with RNase H to remove the ribonucleic acid segment of the extended primer (Column 3 lines 30-40, column 4 lines 25-28, and Figure 5). Scheele teaches that the method can by adapted to permit amplification of the sample of dsDNA by PCR methodology (column 8 lines 58-60). Scheele teaches that the reagents of the RNA primer, DNA target, dNTPs and Taq are placed into a PCR machine with the appropriate number of PCR temperature cycles (column 8 lines 65-69). Therefore in a PCR cycle the resultant dsDNA of step c would be denatured such that multiple copies of the DNA could be copied from the DNA of interest.

With regard to Claim 147, Scheele teaches that the primer can include DNA and RNA (Column 3 lines 40-45).

With regard to Claim 148, Scheele teaches that the primer includes a portion with is complementary to a portion of the oligonucleotide tail added to the 3' end of the target DNA template (column 3 lines 25-35). Therefore the primers include a sequence which is complementary to the tail and therefore noncomplementary to the sequence of the

DNA molecule of interest (e.g. the tail is added to the DNA target of interest) (Figure 5 and column 3 lines 25-40).

Scheele et al. teaches a method of producing copies of a DNA molecule using polymerase and RNase H, however, does not teach method steps of reverse transcriptase having Rnase H activity.

Schuster et al. teaches a method of amplification of nucleic acid molecules (abstract). With regard to Claim 146, Schuster et al. teaches that transcription can be done with a reverse transcriptase that has RNase H activity (column 8 lines 17-24).

Therefore it would be prima facie obvious to one of ordinary skill in the art to modify the method of Scheele et al. to replace the step of adding a polymerase and RNase H to the nucleic acid sample for a step of adding reverse transcriptase with RNase H activity as taught by Schuster et al. with a reasonable expectation of success. The ordinary artisan would be motivated to replace the step of adding a polymerase and RNase H to the nucleic acid sample for a step of adding reverse transcriptase with RNase H activity as taught by Schuster et al. because Schuster et al. teaches that if an enzyme with RNase H activity is used it is possible to omit a separate RNase H digestion step (Column 8 lines 17-24). Therefore the use of reverse transcriptase with RNase H activity would allow the ordinary artisan to perform the method of Scheele et al. with a reduced number of method steps because only reverse transcriptase with RNAse activity must be added to the target to initiate transcription rather than a polymerase and RNase H and thereby allow for a quicker production of DNA molecules.

Response to arguments

The reply traverses the rejection. A summary of the arguments made in the reply are summarized below with response to arguments following.

The reply asserts that that the combination of reference cited provides no description that an extended primer is made from a primer comprising an RNA segment which can be digested by RNase H to allow anther binding and extension event (p. 30 1st paragraph). The reply asserts that the claims have been amended to more clarify that it is the removal of the RNA which is the causative agent that allows another primer binding event and creation of another copy of the DNA molecule of interest (p. 30 1st-2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

With regard to claim 146, step c of the claim includes producing at least one copy of the DNA molecule by extension of the primer under isostatic conditions and then step d is removing the ribonucleotides from the RNA segment by reverse transcriptase to regenerate the primer binding site on said DNA molecule and thereby produce more than one copy of the DNA molecule. The applicant seems to be asserting that the production of the multiple DNA copies is preformed in step d after the addition of the reverse transcriptase, however, based on the teaches of step c it appears that the DNA copies are produced in step c. The way the claim is written encompasses a interpretation that the DNA copies are made in step c (e.g. the PCR step of Scheele et al) and then the RNA is removed to regenerate the primer binding site (e.g. the step of RNase H of Scheele et al). Therefore although the primer binding site is available to another binding event, the multiple copies are actually produced in step c. Step d does

not require that another copy of the DNA molecule be produced after the addition of the reverse transcriptase.

13. Claims 133-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al. (US Patent 5169766 December 8, 1992) in view of Vary et al. (US Patent 4851331).

With regard to Claim 133, Schuster et al. teaches amplification of RNA (abstract). With regard to step a, Schuster et al. teaches a nucleic acid sample containing a RNA molecule of interest (Figure 2 1st step).

With regard to step b, Schuster et al. teaches contacting the RNA molecule with nucleic acid precursors (Column 7 lines 60-65). Schuster et al. teaches annealing primers which are complementary to the RNA molecule of interest (Figure 2), however, does not teach that these primers have an at least one ribonucleic acid segment. Schuster et al. teaches addition of a nucleic acid producing catalyst (e.g. DNA polymerase) (Figure 2). Schuster et al. teaches the addition of RNase H (Figure 2).

With regard to step c, Schuster et al. teaches a DNA copy form the RNA molecule of interest by binding of the primer (Figure 2 step 3).

With regard to step d, Schuster et al. teaches that the first DNA copy (e.g. the cDNA) is used a template to produce a double stranded nucleic acid (e.g. double stranded DNA).

With regard to step e, Schuster et al teaches destroying RNA with RNase H to produce the first DNA double strand copy. Schuster et al. teaches that RNA is

transcribed and that the process can be continued to amplify multiple copies of the RNA molecule of interest (Figure 2).

With regard to Claim 134, Schuster et al. teaches a method wherein the primers comprise nucleotides (e.g. unmodified) (column 5 lines 55-60).

With regard to Claims 135-136, Schuster et al. teaches that the primers can comprise regions which can be used as a template for T7 RNA polymerase (column 8 lines 52-53); therefore these regions would encompass at least 1 noncomplementary nucleotides to the target.

With regard to Claims 138-139, Schuster et al. teaches the use of E. coli DNA polymerase I and Klenow polymerase (column 7 lines 15-20).

With regard to Claim 140, Schuster et al. teaches the use of Taq polymerase (column 7 lines 15).

However, Schuster et al. does not teach that the primer is comprised of RNA segments.

With regard to Claims 133 and 137, Vary et al. teaches that when using a primer-dependent DNA polymerase of eukaryotic origin primers having a 3' terminal ribonucleotide rather having a 3' terminal deoxynucleotide are more active (Column 9 lines 65-69 and column 10 lines 1-10). Vary et al. teaches that oligonucleotides can be comprised of both RNA and DNA (column 10 lines 5-10). The polymerase of Schuster et al. is E. coli DNA polymerase I which is a polymerase of eukaryotic origin.

It would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Schuster et al. to use a RNA/DNA primer as taught

by Vary et al. in place of the DNA primer used to transcribe the RNA to cDNA. The ordinary artisan would be motivated to use a DNA primer with an end of ribonucleotide in order to have a more active elongation of the template region using E. coli DNA polymerase I. Vary et al. teaches that when using a primer-dependent DNA polymerase of eukaryotic origin primers having a 3' terminal ribonucleotide rather having a 3' terminal deoxynucleotide are more active (Column 9 lines 65-69 and column 10 lines 1-10).

Response to arguments

The reply traverses the rejection. A summary of the arguments made in the reply are summarized below with response to arguments following.

The reply asserts that the combination cited does not teach the removal of RNA segments of an extended primer to generate a primer binding site (p. 32 1st paragraph). The reply asserts that that step e of claim 133 requires the nuclease digestion of the extended primer after conversion of the first extended primer (the first DNA copy) into double stranded form in step d (p. 32 2nd paragraph). The reply assert that there is no description in Schuster et al. for treating a ads DNA molecule (the product of step d) with an RNase H as is required by step e (p. 32 2nd full paragraph).

The reply asserts that with regard to Vary et al. there is no benefit for a primer binding event after excision of a nucleotide as described in the Vary parent, and that the only benefit that is conveyed is that the use of ribonucleotide in the 3'end can offer superior extension characteristics when a eukaryotic derived polymerase is used (p. 32

3rd paragraph). The reply asserts that there is no particular advantage described or suggested to be endowed by the presence of one or more ribonucleotide moieties after it has been extended in Vary et al. (p. 32 3rd full paragraph). The reply asserts that this is in contrast with the instant claims which enjoy its properties by elimination of ribonucleotides after an extension of a primer with an RNA segment has taken place (p. 32 3rd full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that Schuster et al. does teaches the removal of the RNA segments and therefore teaches the regeneration of the primer binding site. Schuster et al teaches destroying RNA with RNase H to produce the first DNA double strand copy (Figure 2). Schuster et al. teaches that RNA is transcribed and that the process can be continued to amplify multiple copies of the RNA molecule of interest (Figure 2). Therefore Schuster et al. teaches using RNase H to generate a primer binding site on a said copy and that more that one copy is produced. As such Schuster teaches all the required limitations of the claims.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

/Sarae Bausch/
Primary Examiner, Art Unit 1634